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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/540,343	10/06/1995	DENNIS E. HALLAHAN	ARCD:194	8900

7590 11/29/2001

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EXAMINER
PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 11/29/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/540,343	Applicant(s) HALLAHAN ET AL.	
	Examiner Scott Priebe	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/19/01, the decision by the Board* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10,11,13,15,18-27 and 35-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10,11,13,15,18-27 and 35-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Upon review and consideration of the decision by the Board, the rejection under 35 USC 112, first para. is withdrawn. However, the finality of the Office action of 7/8/97 is withdrawn and prosecution is re-opened in light of newly discovered prior art, as indicated below. The amendments filed 9/11/97 and 3/5/98 have been entered as previously indicated.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 depends from itself, and is incomplete. There are no active process steps recited.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 8, 10, 11, 13, 15, 18-27 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Martuza et al., US 5,585,096, filed 7/94 - hereafter Martuza A.

Martuza A discloses various methods of using attenuated or recombinant herpes simplex virus, including HSV-1, for killing tumor cells *in vivo* in a mammal or human in treatment of brain cancer and breast cancer *inter alia*. In a preferred embodiment, the methods are combined with conventional radiotherapy. The HSV is delivered by direct intraneoplastic inoculation or orally. See entire reference, especially Summary of Invention, col. 3-4; and col. 11, line 64 to col. 13, line 7

Claims 8, 10, 11, 13, 15, 18-27 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Martuza et al., US 5,728,379 (filed 6/1995 and claiming priority to US 5,585,096, filed 7/94) - hereafter Martuza B.

Martuza B discloses various methods of using attenuated, recombinant herpes simplex virus, including HSV-1, for killing tumor cells *in vivo* in a mammal or human in treatment of brain cancer and breast cancer *inter alia*. The HSV has a tumor- tissue- or cell-specific promoter operatively linked to an essential HSV gene. In a preferred embodiment, the methods are combined with conventional radiotherapy. The HSV is delivered by direct intraneoplastic inoculation or orally.

See entire reference, especially Summary of Invention, col. 4-6; col. 28, lines 15-36; claims, col. 41-42.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 35-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCormick, US 5,846,945 (filed 6/1995, claiming priority to applications filed 2/1994 and 2/1993) in view of a) either Martuza A or Martuza B, or b) Frisch, US 5,776,743 (filed 9/1994); or c) Frisch and either Martuza A or Martuza B.

McCormick describes various methods of using oncolytic mutant adenoviruses, including Ad5, for killing tumor cells *in vivo* in a mammal or human in treatment of a variety of cancers, including breast cancer. The adenovirus is delivered by a variety of methods depending on application, including orally and by intratumoral injection. In a preferred embodiment, the methods are combined with conventional antineoplastic protocols, such as chemotherapy. The adenoviruses have mutations in E1A, E1B, or both E1A and E1B, depending on the specific application based on whether the tumor cells lack retinoblastoma protein, p53, or both, and are not required to have an exogenous therapeutic gene. See entire reference, especially col. 9-14; col. 16, line 40 to col. 18, line 29; claims, col. 20. McCormick does not explicitly teach that radiotherapy is considered a conventional antineoplastic protocol to be combined with the oncolytic viral therapy.

However, Martuza A and Martuza B, as described above, described a similar method using HSV as the oncolytic virus for killing tumor cells, primarily of nervous system tissue, and taught that is was preferred to combine the oncolytic viral therapy with other conventional antineoplastic therapies, including radiotherapy.

Also, Frisch described a method for killing tumor cells in treatment of cancer involving delivery of nucleic acid encoding the adenoviral E1A protein, e.g. from Ad5, to tumor cells, followed by radiation therapy. The adenoviral E1A protein selectively sensitizes tumor cells to radiation, independent of p53 expression in the tumor cells. Frisch disclosed that the nucleic acid encoding the adenoviral E1A protein could be delivered by a variety of means, including viral

infection, presumably adenoviral infection. See entire reference, especially the Abstract; col. 2, line 65 to col. 5, line 30; claims 5 and 6, col. 18.

Therefore, it would have been obvious to one of ordinary skill in the pertinent art at the time the instant invention was made to have combined the oncolytic adenoviral method for killing tumor cells of McCormick with conventional radiotherapy. McCormick teaches to combine the adenoviral method with conventional antineoplastic therapies, and Martuza A and Martuza B disclose that radiotherapy is a preferred antineoplastic therapy to combine with oncolytic viral therapy. In addition, Frisch teaches the added benefit for the E1B-mutated adenovirus of McCormick that retain the adenoviral E1A region, that the E1A protein encoded would further sensitize the tumor cells to radiation in a p53-independent pathway. The expectation of success is more than reasonable given that McCormick teaches how to make and administer the adenovirus in an effective manner and radiotherapy was an already established method of anti-cancer therapy. One would expect the combination therapy to provide at least an additive increase is effectiveness of tumor cell killing over either therapy alone since the mechanisms of cell killing by oncolytic viral therapy and radiation are different. The disclosure of Frisch would suggest that for the case of adenovirus retaining E1A, the effect of the combined therapy might be synergistic due to the radiosensitization of tumor cells by E1A proteins. Consequently, the invention as a whole is *prima facie* obvious.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Primary Examiner
Technology Center 1600
Art Unit 1632